PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00	A1	(11) International Publication Number: WO 95/05804
		(43) International Publication Date: 2 March 1995 (02.03.95)

(21) International Application Number: PCT/US94/02023

(22) International Filing Date: 16 February 1994 (16.02.94)

(30) Priority Data:
PCT/US93/07859 20 August 1993 (20.08.93) WO
(34) Countries for which the regional or international application was filed: AT et al.

(71) Applicant: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US).

(72) Inventors: ALI, Yusuf; 6904 Wicks Trail, Forth Worth, TX 76133 (US). REED, Kenneth, W.; 1241 Fairfax Hunt, Lawrenceville, GA 30243 (US).

(74) Agents: RYAN, Patrick et al.; Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: TOPICAL OPHTHALMIC PHARMACEUTICAL VEHICLES

(57) Abstract

Universal ophthalmic pharmaceutical vehicles which increase in viscosity upon instillation in the eye are disclosed. Ophthalmic compositions of the universal vehicle and a pharmaceutically active drug are also disclosed. In one embodiment, the vehicle gels upon instillation in the eye. In another embodiment, suspension vehicles having superior physical stability are provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

TOPICAL OPHTHALMIC PHARMACEUTICAL VEHICLES

This application is a continuation-in-part of U.S. Serial No. 08/109,748, filed August 20, 1993, currently copending, which is a continuation-in-part of U.S. Serial No. 07/913,110, filed July 14, 1992, now abandoned, which is a continuation-in-part of U.S. Serial No. 07/414,550, filed September 28, 1989, now abandoned.

Background of the Invention

This invention is directed to liquid ophthalmic pharmaceutical vehicles which become viscous on contacting the eye. This invention also relates to topical ophthalmic compositions comprising the vehicle and a pharmaceutically active drug.

It is known that the addition of viscous or visco-elastic polymers to an eye drop pharmaceutical composition will increase the viscosity of the composition. This is usually desirable on the premise that an increased vehicle viscosity enhances drug delivery and duration of action; see, for example, J. Pharm. Pharmacol., Vol.34, pp.464-466 (January 7, 1982). However, it is frequently advantageous to administer ophthalmic compositions as a drop, that is, an aqueous solution or suspension rather than a thick, viscous gel or ointment which can be messy and may tend to blur vision. In addition, non-droppable compositions can present problems with patient compliance, especially with the elderly.

Another problem, in the case of suspension compositions, is their poor physical stability. Many marketed ophthalmic suspension products currently use the polymers hydroxypropyl methylcellulose, hydroxyethyl cellulose, and polyvinyl alcohol to increase the suspension's viscosity and thus decrease the settling rate of the drug particles. These suspensions are not well flocculated and, with time, the insoluble drug particles will completely settle forming a dense layer which will not resuspend easily. This in turn may undesireably lead to variable drug dosages.

Summary of the Invention

The present invention provides for ophthalmic vehicles and compositions which can be administered as a drop, but whose viscosity increases upon instillation into the eye so that the composition provides for relatively better drug delivery and duration of action, referred to herein as bioavailability, of drug over aqueous compositions whose viscosity does not increase upon instillation. In one embodiment the vehicle gels upon instillation. In another embodiment, the vehicle provides an improved suspension vehicle.

This invention relates to ophthalmic pharmaceutical vehicles and compositions comprising the vehicle and a pharmaceutically active drug in which the vehicle comprises a charged polymer and oppositely charged electrolytes or molecules, hereinafter referred to collectively as "electrolytes", which can be administered as a drop and upon instillation, increase in viscosity. The polymer can be negatively charged, such as a carboxyvinyl polymer, in which case the vehicle will include positively charged electrolytes, such as calcium. Conversely, the polymer can be positively charged and then negatively charged electrolytes are used in the vehicle.

The suspension vehicles of the present invention possess improved suspension characteristics. They exhibit superior physical stability and permit easy resuspension of insoluble drug particles, thus resulting in greater uniformity of drug dosing. In addition to an ophthalmic dosage form, the vehicles and compositions of the present invention also provide for oral, parenteral and topical suspension dosage forms.

The vehicles of this invention can be used in composition with pharmaceutically active drugs. The term "drug", as used herein, means any therapeutic agent that is desirable to deliver to the eye. There is no limitation on the type of drug which can be incorporated into the compositions disclosed herein. The drugs can be charged, uncharged, water soluble or insoluble.

Detailed Description of Preferred Embodiments

The vehicles disclosed herein comprise a charged polymer and oppositely charged electrolytes. Without intending to be bound by any theory, it is understood that the vehicle's viscosity is increased due to the decrease in electrolyte concentration when the vehicle is administered to the eye. In the case of a gelling vehicle, the concentrations of the polymer and electrolytes in the vehicle are optimal when a small change in electrolyte concentration will result in a dramatic increase in vehicle viscosity. The small change in electrolyte concentration on instillation is caused by the electrolytes being taken up by the cells in the eye, by diffusing out of the polymer vehicle or being eliminated in tear fluid or by a combination of these mechanisms. Whatever the mechanism, the concentration of electrolytes in the vehicle is reduced and the vehicle viscosity increases.

As used herein, "gels" means the vehicle's viscosity increases sufficiently to transform the drop into a semi-solid or gelatinous state.

Polymers which can be used in the vehicle disclosed herein include any nontoxic charged water soluble polymer. These polymers can either be negatively or positively charged. Typically, negatively charged polymers will include, but are not limited to, carboxy vinyl polymers, such as Carbopol®, sodium carboxy methylcellulose, pectin, gelatin (Type B), sodium hyaluronate, acacia, calcium carboxy methylcellulose, sodium alginate and polystyrene sulfonic acid (PSSA). These polymers are used in the vehicles at concentrations from about 0.1 to about 10.0 weight percent (wt.%).

Electrolytes which are used in conjunction with the charged polymers will be either cations or anions depending on the charged polymer being used. If negatively charged polymers are being used in the vehicle the electrolytes which are used to provide for the changing viscosity upon instillation will be positively charged. These cations will typically be Na^+, K^+, Mn^{++}, Ca^{++}, Mg^{++}, Fe^{++}, Fe^{+++}, Al^{+++}, Li^+, Zn^{++} and Be^{++}. In addition, positively charged organic ions can be used, for example,

lysine•HCl, arginine•HCl and histadine•HCl. These electrolytes will typically be present at a concentration of between 0.01 and 1.0 wt.%.

If a positively charged polymer is used, such as gelatin (Type A) or polyvinyl amine, the electrolyte used in conjunction therewith to provide for viscosity changes will be an anion. These anions will typically be PO_4^{-3}, HPO_4^{-2}, $H_2PO_4^-$, I^-, Cl^-, F^-, SO_4^{-2}, HCO_3^- and negatively charged organic ions. Again, the polymer concentration will range from about 0.1 - 10.0 wt.% and the electrolytes will typically be present at a concentration of between about 0.01 wt.% to about 1.0 wt.%.

The concentrations of the polymers and corresponding electrolytes in the vehicles of the present invention are adjusted to provide for compositions in which the viscosity is such that the composition can be administered as a drop topically (typically, about 200 to about 2000 cps.). Upon instillation in the eye, the electrolyte concentration will change resulting in an increase in viscosity. The resulting compositions allow for the delivery of a drug in drop form, but provide for enhanced drug delivery due to the compositions' increased viscosity once in the eye. Depending on the specific combination of polymer and electrolyte concentration, in conjunction with any other ingredients, such as the drug, the small change in electrolyte concentration which occurs upon instillation in the eye may provide for a large increase in viscosity such that the vehicle gels. If the concentration level of polymer to electrolyte is too high, the vehicle will not be easily administrable as a drop. Conversely, it is too low, the vehicle will not undergo any significant viscosity increase upon instillation.

An impoved suspension vehicle is obtained when the polymer to electroylte concentration is low. Although such vehicles may not experience an increase in viscosity sufficient to transform the vehicle into a gel upon instillation, they do exhibit superior physical stability. The polymer acts to flocculate the insoluble particles by providing a stearic barrier and the electrolytes act to decrease the viscosity of the vehicle to about 200 cps or less, typically to about 200 cps or less, typically to about 75 cps to 150 cps, for easy dispensability from a plastic drop dispensing bottle. The

insoluble particles may be resuspended easily for uniform dosing. Compositions containing a water-insoluble drug compound which possess such relatively low polymer and electrolyte concentration levels do exhibit superior physical stability, however. The polymer acts to flocculate the insoluble particles and the electrolytes act to decrease the viscosity of the vehicle. The insoluble particles may be resuspended easily for uniform dosing and can be dispensed from a plastic drop dispensing bottle.

Preferably, the polymers are negatively charged in both cases above, and more preferably, the polymers are the carboxy vinyl polymers available from B.F. Goodrich under the product name Carbopol®. Most preferred are the Carbopol® 934P polymers. The corresponding preferred electrolytes are therefore positively charged. Most preferred are the Na^{+}, Ca^{++}, and Al^{+++} cations. Most preferred for gelling vehicles are Ca^{++}, Mg^{++}, Zn^{++}, and Al^{+++}. Most preferred for suspension vehicles are Na^{+}, Zn^{++}, and Al^{+++}.

Carbopol® is particularly preferred for the ophthalmic vehicles of the present invention because it has low ocular toxicity, it is an effective polyelectrolyte when neutralized in the pH range near seven, it is a long chain polymer which may adsorb onto the surface of suspended particles, thus providing stearic hindrance to the particles agglomerating, and the viscosity of formulations containing Carbopol® is easily optimized through the use of positively charged species. In this preferred case where the polymer is Carbopol®, the maximum concentration of polymer in the vehicles of the present invention will be approximately 3 wt.% or less.

The vehicles of this invention may be used as carriers for a wide variety of pharmaceutically active, water-insoluble drugs; these vehicles may therefore be called "universal" ophthalmic vehicles. Drugs which can be delivered in the vehicles of the present invention include, but are not limited to, steroids, growth factors, antioxidants, aldose reductase inhibitors, non steroidal antiinflammatories, immunomodulators, anti-allergics, antimicrobials, and beta-blockers. If the drug particles are charged, the concentrations of the polymer and electrolyte are adjusted so that the vehicle's

viscosity allows for topical drop administration. The concentrations of the polymer and corresponding electrolyte are dependant upon the nature of the polymer itself, the nature of the drug/polymer charge interaction or lack thereof, the desired amount of drug retention time in the eye and, in the case of a suspension, whether the vehicle is optimized for physical stability or viscosity increase upon instillation.

In addition to the principal active ingredients, the vehicles and compositions of the present invention may further comprise various formulatory ingredients, such as anti-microbial preservatives and tonicity agents. For example, antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methylparaben, propylparaben, phenylethyl alcohol, EDTA, Hamposyl®, sorbic acid, Polyquad® and other agents equally well known to those skilled in the art. Such preservatives, if employed, will typically be used in an amount from about 0.0001 wt.% to 1.0 wt.%. Suitable agents which may be used to adjust tonicity or osmolality of the compositions include: mannitol, dextrose, glycerine and propylene glycol. If used, such agents will be employed in an amount of about 0.1 wt.% to 10.0 wt.%. However, preferable composition of the present invention will not include preservatives or tonicity agents which are known to adversely affect or irritate the eye, particularly the cornea.

The following Examples illustrate certain embodiments of the vehicles and compositions of this invention and are not intended to limit the scope of the present invention in any way.

Examples 1-4: Universal ophthalmic gelling vehicles which are administrable as a drop, but which gel upon instillation in the eye. If charged drug particles are added to these vehicles, the electrolyte concentration may have to be adjusted so that the composition remains administrable as a drop but gels upon instillation.

Example 1

"Universal" Ophthalmic Vehicle No. 1

Ingredient	Weight Percent
Carbopol® 934P	0.30
Calcium Chloride	0.045
Mannitol	4.50
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

Preparation

The recommended compounding procedure for preparing "Universal" Ophthalmic Vehicle No. 1 is as follows:

1. Tare a labeled vessel, weight the Carbopol® into the vessel and begin agitation.
2. Add the remaining ingredients and stir until well dispersed.
3. Add sufficient purified water to adjust the weight to 80% of total batch weight.
4. Adjust the pH to 7.2 + 0.2 using only sodium hydroxide. Use hydrochloric acid only if absolutely necessary, and they in the smallest quantities need to obtain the target pH range.
5. QS to 100% of the final batch weight with purified water.
6. Steam sterilize the formulation.

The vehicles of Examples 2-6 were also prepared according to this compounding procedure.

Example 2

"Universal" Ophthalmic Vehicle No. 2

Ingredient	Weight Percent
Carbopol® 934P	0.40
Calcium Chloride	0.10
Mannitol	4.00
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

Example 3

"Universal" Ophthalmic Vehicle No. 3

Ingredient	Weight Percent
Carbopol® 934P	0.40
Calcium Chloride	0.05
Lysine HCl	0.225
Mannitol	4.00
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

Example 4

"Universal" Ophthalmic Vehicle No. 4

Ingredient	Weight Percent
Carbopol® 934P	1.00
Calcium Chloride	0.40
Mannitol	3.00
KOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

Examples 5-6: Universal ophthalmic pharmaceutical suspension vehicles which exhibit superior physical stability. If charged drug particles are added to these suspension vehicles, an appropriate adjustment may have to be made to the electrolyte concentration.

Example 5

"Universal" Pharmaceutical Vehicle No. 1

Ingredient	Weight Percent
Mannitol	1.80
Carbopol® 934P	0.45
Polysorbate 80	0.05
Sodium Chloride	0.50
Edetate Disodium	0.01
Benzalkonium Chloride	0.01 + 5% excess
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

Example 6

"Universal" Pharmaceutical Vehicle No. 2

Ingredient	Weight Percent
Carbopol® 934p	0.70
Polysorbate 80	0.05
Sodium Chloride	0.80
Edetate Disodium	0.01
Benzalkonium Chloride	0.01 + 5% excess
NaOH	pH 7.2 ± 0.2
Purified water	q.s. 100%

Example 7

Preferred Ophthalmic Gelling Solution

Ingredient	Weight Percent
Betaxolol HCl	.28
Carbopol® 934P	1.00
Calcium Chloride	.75
Mannitol	1.5
Benzalkonium Chloride	0.01
EDTA	.05
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

Example 8

Preferred Suspension Composition

Ingredient	Weight Percent
Rimexolone	1.0
Mannitol	1.80
Carbopol® 934P	0.45
Polysorbate 80	0.05
Sodium Chloride	0.50
Edetate Disodium	0.01
Benzalkonium Chloride	0.01 + 5% excess
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

The results of a sedimentation/settling study comparing the physical stability of the Rimexolone steroid suspension of Example 8 to the commercially available prednisolone acetate steroid suspension (1 wt.%), Econopred®, are shown below in Table 1. The Econopred® suspension contains hydroxypropyl methylcellulose as its polymeric viscosity enhancer. As indicated above, Example 8 contains Carbopol® as its stearic stabilizer and viscosity enhancer. After standing for six months in a measuring glass cylinder, 2% of the Econopred® suspension settled to the bottom as a cake or sediment. The remaining 98% consisted of a single supernatant phase. In contrast, none of the suspension of Example 8 settled to the bottom as a cake or sediment after standing for six months. Substantially all of the suspension of Example 8 remained flocculated (98%), topped with approximately a 2% supernatant layer. The suspension composition of Example 8 will return to its fully redispersed state after less than 5 seconds of gentle shaking by hand.

We claim:

1. A topical ophthalmic vehicle comprising:
a negatively charged polymer selected from the group consisting of carboxy vinyl polymers, sodium carboxy methylcellulose, pectin, gelatin (Type B), sodium hyaluronate, acacia, calcium carboxy methylcellulose, sodium alginate and polystyrene sulfonic acid; and a positively charged electrolyte selected from the group consisting of Na^+, K^+, Mn^{++}, Ca^{++}, Mg^{++}, Fe^{++}, Fe^{+++}, Al^{+++}, Li^+, Zn^{++}, Be^{++}, lysine•HCl, arginine•HCl and histadine•HCl; and wherein the concentrations of the polymer and the electrolyte are such that the vehicle is administrable as a drop and increases in viscosity upon instillation in the eye.

2. The vehicle of Claim 1 wherein the polymer concentration is from about 0.1 to about 10 wt.%.

3. The vehicle of Claim 2 wherein the polymer concentration is from about 0.1 to about 3 wt%.

4. The vehicle of Claim 1 wherein the electrolyte concentration is from about 0.01 to about 1 wt%.

5. The vehicle of Claim 1 wherein the polymer is a carboxy vinyl polymer.

6. The vehicle of Claim 5 wherein the polymer is Carbopol® carboxy vinyl polymer.

7. The vehicle of Claim 1 wherein the electrolyte is selected from the group consisting of Na^+, Ca^{++}, and Al^{+++}.

8. The vehicle of Claim 1 wherein the increase in viscosity upon instillation transforms the vehicle into a gel.

9. A pharmaceutical suspension composition which remains at least about 95% flocculated after standing for six months which comprises: a pharmaceutically active, water-insoluble drug and a suspension vehicle,

wherein the suspension vehicle comprises a negatively charged polymer selected from the group consisting of carboxy vinyl polymers, sodium carboxy methylcellulose, pectin, gelatin (Type B), sodium hyaluronate, acacia, calcium carboxy methylcellulose, sodium alginate and polystyrene sulfonic acid; and a positively charged electrolyte selected from the group consisting of Na^{+}, K^{+}, Mn^{++}, Ca^{++}, Mg^{++}, Fe^{++}, Fe^{+++}, Al^{+++}, Li^{+}, Zn^{++}, Be^{++}, lysine∘HCl, arginine∘HCl and histadine∘HCl; and wherein the concentrations of the polymer and the electrolyte are such that the vehicle is administrable as a drop and increases in viscosity upon instillation in the eye.

10. The suspension composition of Claim 9 wherein the polymer is Carbopol® and the electrolyte is selected from the group consisting of Na^{+}, Ca^{++}, and Al^{+++}, and wherein the amount of Carbopol® is from about 0.1 to about 3 wt% and the amount of electrolyte is from about 0.01 to about 1 wt%.

11. A topical ophthalmic vehicle administrable as a drop which increases in viscosity upon instillation in the eye comprising:
Carbopol® carboxy vinyl polymer and an electrolyte selected from the group consisting of Na^{+}, Ca^{++}, and Al^{+++}, wherein the amount of Carbopol® is from about 0.1 to about 3 wt% and the amount of electrolyte is from about 0.01 to about 1 wt%.

12. A topical ophthalmic vehicle administrable as a drop which increases in viscosity upon instillation in the eye comprising:
a positively charged polymer selected from the group consisting of gelatin (Type A) and polyvinyl amine; and a negatively charged electrolyte selected from the group consisting of PO_4^{-3}, HPO_4^{-2}, $H_2PO_4^{-}$, I^{-}, Cl^{-}, F^{-}, SO_4^{-2}, HCO_3.

13. The vehicle of Claim 12 wherein the polymer concentration is from about 0.1 to about 10 wt.%.

14. The vehicle of Claim 13 wherein the polymer concentration is from about 0.1 to about 3 wt%.

15. The vehicle of Claim 12 wherein the electrolyte concentration is from about 0.01 to about 1 wt%.

16. The vehicle of Claim 12 wherein the increase in viscosity upon instillation transforms the vehicle into a gel.

17. A method delivering a drug to the eye which comprises:
topically administering a composition comprising a charged polymer and an oppositely charged electrolyte at concentrations such that the composition is administrable as a drop and gels upon instillation.

18. The method of Claim 17 wherein the polymer is carboxy vinyl polymer and the electrolyte is selected from the group consisting of Na^{+}, CA^{++}, and Al^{+++}.

19. The method of Claim 18 wherein the polymer is Carbopol® carboxy vinyl polymer.

INTERNATIONAL SEARCH REPORT

Inten ial Application No
PCT/US 94/02023

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,89 06964 (INSITE VISION INC.) 10 August 1989 see claims 1,2,7,8 see page 4, line 20 - page 5, line 27 see page 9, line 6 - page 10, line 22 see page 11, line 3 - page 12, line 13 see example 11 -----	1-11, 17-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 1994	13.09.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In. .ational application No.
PCT/US 94/ 02023

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: ALTHOUGH CLAIMS 17-19 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOSITION.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 94/02023

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8906964	10-08-89	DE-T-	68907545	28-10-93
		DK-B-	168727	30-05-94
		EP-A,B	0362321	11-04-90
		JP-T-	2503201	04-10-90
		US-A-	5192535	09-03-93
		US-A-	5188826	23-02-93